REMARKS/ARGUMENTS

Status of Claims

Claims 1-6 are pending in this application. Claim 6 has been cancelled. As such, claims 1-5 are currently under consideration.

Amendments to claims

Claims 1 and 2 have been amended to recite that the claimed suppressor cells are CD4+CD25+ cells. This amendment is fully supported throughout the specification, for example, in Figure 6. As such, these amendments add no new matter.

Claim 4 has been amended to clarify the point at which PBMCs are enriched for CD4+ cells. This amendment adds no new matter, and is fully supported in the specification, for example, in paragraphs [0048] through [0058] of the published application. As such these amendments add no matter.

Applicants request entry of the claims as amended into the record.

Rejection Under 35 U.S.C. § 102(e)

Claims 1-3 and 6 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by McIntosh U.S. Patent No. 6,685,936 ("McIntosh"). Applicants respectfully disagree.

To maintain a *prima facie* case of anticipation, the Examiner must demonstrate that each and every element as set forth in the claim is either expressly found or is inherently described in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the ...claim. *see MPEP § 2131.* Applicant submits that the identical invention is not shown in the reference as is contained in the claim. Specifically, the cells described in McIntosh are not the same cells as those of the instantly claimed invention. Therefore, Applicant respectfully traverses this rejection.

The cells produced by the methods of McIntosh are not identical to the cells of the instantly claimed invention. As the Examiner notes in the Office Action of October 10, 2006, McIntosh "does not teach the same process of making the claimed suppressor T cells." *Office*

Action, p.2. The processes described in McIntosh result in a population of suppressor T cells which does not have identical characteristics to the cells of the instantly claimed invention. As noted in the Horwitz declaration submitted in the response to office action filed August 21, 2006, the suppressor T cells of McIntosh require the presence of CD8+ cells to maintain their suppressor activity. In contrast, the suppressor cells of the instantly claimed invention do not require the presence of CD8+ cells to have suppressive activity.

The Examiner asserts that the instant claims encompass a population of suppressor T cells generated by culturing enriched CD8+ T cells. Solely to further prosecution of this application, Applicants have amended the claims to remove all reference to CD8+ cells. As such, the Examiner's statement on page 3 of the current Office Action that the CD8+ cells are required as a starting material is moot. Applicants also note that although the claimed processes *can* induce CD8+ T cells to exhibit suppressor activity, the presence of CD8+ T cells is not *required* for the suppressor activity exhibited by the claimed suppressor cells. As disclosed in Example 1 of the application, CD4+ cells were isolated from the recipient and activated with TGF-β. CD8+ cells were not present in the system during the process of generating suppressor cells from these isolated CD4+ cells. Figures 2A through 4B show that the T cells generated using the disclosed process are able to block the ability of the recipient's T cells to kill donor cells, even without the presence of CD8+ cells. This is in contrast to what is shown in McIntosh, where the disclosed suppressor cells are specifically described as requiring the presence of CD8+ cells. *see Column 8, lines 19ff.* McIntosh discloses that depletion of CD8+ cells resulted in only "partial suppression", and further makes the statement that the suppressor cells induced by the disclosed methods were CD8+ cells. Thus, the cells of McIntosh require the presence of CD8+ cells, which is not the case for the instantly claimed invention. As such, the cells of McIntosh cannot be identical to those of the instant claims.

Since the cells disclosed in McIntosh are not identical to the claimed cells, a rejection under §102 is improper, and Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-5 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hall et al. *J. Exp. Med.*, 171:141-157 (1990), ("Hall"). Applicants respectfully disagree.

The suppressor cells in Hall require the presence of CD8+ cells, which, as discussed above, are not required for the suppressive activity of the cells of the instantly claimed invention. Table IV of Hall shows CD4+ suppressor cells can maintain tolerance to a foreign heart graft in adult animals that have been irradiated and thymectomized, and Hall speculates that the CD4+ cells may exert suppressive activity by themselves. However, in the data in Table V, Hall clearly shows that radioresistant CD8+ cells are required for the CD4+ suppressor cells to function, and on the next page, Hall explicitly states: "Taken together, these results show the rejection response in irradiated rats is inhibited by an MRC Ox8+ cell that was radioresistant but not thymus derived. This cell was critical for the transfer of suppression by the W3/25+ cells from CSA-treated hosts." *emphasis added, Hall, p.148, second full paragraph.* (Note that the MRC Ox8+ cells in Hall are CD8+ cells—see page 143 of Hall, first full paragraph). Hall clearly concludes that the CD4+ cells in its system require the presence of CD8+ cells to mediate suppressive activity. As the instantly claimed cells do not require the presence of CD8+ cells to have suppressive activity, the cells in Hall cannot be identical to those of the instantly claimed invention.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-5 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Groux et al. ("Groux"), in view of Seder et al. ("Seder"). Applicants respectfully disagree.

When rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. *MPEP § 2142.* The inquiry of obviousness is controlled by the Graham factors. *See KSR International Co. v. Teleflex Inc.* 1727 S.C.t (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966)). These factors are: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness. Applicants maintain that the combination of Groux and Seder does not meet the requirements of a finding of obviousness under §103(a).

The cells in Groux and Seder are not the cells of the instantly claimed invention

The cells in Groux are Tr1 cells. The Tr1 cells in Groux are activated by IL-10 and in turn produce high levels of IL-10. *see Groux, Abstract.* These cells have a very short life span

and limited proliferation potential, as is described in the instant application. *see paragraph [0020] of the published application.* In contrast, the suppressor cells of the instant invention are CD4+CD25+ regulatory cells (*see Fig. 6 of the instant application*), which are known in the art to be a distinct subset of T cells from the Tr1 cells of Groux. Included with this response as Exhibit A is a review article by Roncarolo et al., ("Roncarolo"), which states that Tr1 cells are not the same CD4+CD25+ cells. For example, in the Introduction of Roncarolo is the following statement:

> The two most relevant classes of Tregs described within the CD4+ subset are T regulatory type 1 (Tr1) cells...and CD4+CD25+ Tregs. These two Treg subsets differ in a number of important biological features, including their specific cytokine secretion profile, cellular markers, ability to differentiate in response to antigen-specific stimuli, and dependency on cytokines vs. cell-cell contact mechanisms for mediating suppressive activity.... *Roncarolo, pp. 28-29.*

The cells in Groux are clearly a subset of Tregs that are distinct from the suppressor cells of the instantly claimed invention. Thus, a skilled artisan would not expect that the claimed cells could successfully be produced by incubating the cells of Groux with the TGF-β described in Seder. The Examiner cites Seder for its teaching that incubating CD4+ T cells with TGF-β enhances the production of TGF-β by the T cells. However, again, there is no indication in Seder that its methods produce the presently claimed suppressor cells. In fact, Seder teaches priming of CD4+ T cells with IL-10 (*see Seder, page 5722*), indicating that the cells produced by Seder are the Tr1 cells of Groux rather than the suppressor cells of the instant claims.

In addition, the method used to produce the cells of the instant claims is not taught by the combination of Groux and Seder. The cells of the instantly claimed invention are produced using donor irradiated T-cell depleted mononuclear cells and a regulatory composition comprising TGF-β. Neither Groux nor Seder recite combining their starting cells with donor irradiated mononuclear cells to produce their Tr1 cells. As a result, the combination of Groux and Seder fails to recite every element of the instant claims.

There is no motivation to combine Groux and Seder

Even assuming *inter alia* that the cells of Groux are equivalent to the cells of the instant invention, Applicants submit that the skilled artisan would have no motivation to combine Groux and Seder to practice the instantly claimed invention.

Groux teaches on page 739 that proliferation of the Tr1 clones was augmented by a neutralizing anti-TGF-β monoclonal antibody. Even if the Tr1 cells of Groux were the suppressor cells of the instant invention, the fact that Groux found that blocking TGF-β activity augmented proliferation of these cells essentially teaches away from combining the methods of Groux with the methods of Seder. One of skill in the art would not be motivated to combine Groux with Seder, because Groux teaches that the TGF-β of Seder would work against the goal of inducing and enhancing the proliferation of the Tr1 clones. Seder teaches methods to upregulate the production of TGF-β, which Groux teaches would essentially inhibit proliferation of Tr1 cells. Thus, one of skill in the art would have no expectation of success in practicing the claimed invention by combining these two references.

For at least the foregoing reasons, the combination of Seder and Groux fails to describe the instantly claimed invention, and Applicants request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1225 (direct line).

Although no fees are believed to be due, the Commissioner is hereby authorized to charge any such fees or credit any fees associated with this matter to Deposit Account No. 50-0310 (Attorney Docket No. 067797-5006-US01).

Respectfully submitted,

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Enclosures

Exhibit A: Roncarolo et al., (2006) *Immunological Reviews*, 212:28-50.